

Overview of Lithium's Use: A Nationwide Survey

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Abstract

Background: Lithium is considered the gold standard treatment for bipolar disorder (BD). Its use as a first-line treatment in BD is supported by current clinical guidelines and scientific evidence. However, over the last two decades it has been observed a downward tendency in lithium's use in several developed countries. Based on a nationwide survey, the objective of this study is to analyze in a large sample of psychiatrists relevant issues of the use of lithium salts in BD.

Methods: Data were collected through an anonymous survey sent by email among 500 psychiatrists who belong to a National Society of Psychiatry (Spanish Society of Biological Psychiatry). The survey is a self-administered questionnaire consisting of 21 items on the most key aspects of the use of lithium (indication, dosage, monitoring and information for patients).

Results: 212 psychiatrists completed the survey. 70% of psychiatrists prescribe lithium to more than 50% of patients diagnosed with BD. Adverse effects are the main reason not to use lithium salts. Over 75% of the participants consider lithium salts the treatment of choice for the maintenance phase of BD, both in women and men. Most of the participants (> 50%) start lithium after the first affective episode, use conservative plasma concentrations (0.6-0.8 mmol/L) and generally prescribe it twice a day. 57% of psychiatrists who treat patients under 18 do not use lithium in this population. About 70% of the survey respondents use official protocols to inform and monitor patients who are on lithium treatment.

Conclusions: From the results of the present study it can be concluded that the use of lithium in Spain is in line with the recommendations of the main international clinical guidelines and current scientific literature. The first reason not to prescribe lithium in our country is the perception of its adverse effects and not the aspects related to its practical use or its effectiveness. Considering that BD is a chronic disease that has a typical onset in adolescence, the reasons for the low rate of prescription of lithium salts in patients under 18 must be thoroughly studied.

Introduction

Despite the fact that more than 70 years have passed since the Australian psychiatrist John Cade reported the antimanic efficacy of lithium carbonate (Cade, 1949), the main current clinical guidelines still consider it a first-choice treatment for Bipolar Disorder (BD) (Fountoulakis et al., 2017; Yatham et al., 2018). It has proved effective not only in acute manic episodes (Yildiz et al., 2014), but also in depressive (Malhi et al., 2017) and mixed episodes (Sani and Fiorillo, 2019). Nevertheless, lithium is noted for its outstanding efficacy in the maintenance or prophylactic treatment of BD (Jauhar and Young., 2019; Severus et al., 2018). Bearing in mind the frequent chronic, recurrent and disabling nature of BD (a disease that affects more than 1% of the world population) (Vieta et al., 2019), a long-term treatment which allows preventing relapses or recurrences is vital. In this regard, lithium continues to be the gold standard treatment supported by extensive scientific evidence (Carvalho et al, 2020). Both in controlled clinical trials and observational studies lithium has shown its efficacy and superiority in the prophylaxis

of any type of affective episode (Berk et al., 2017a; González-Pinto et al., 2018; Kessing et al., 2017; Lähteenvuo et al., 2018; Miura et al., 2014; Severus et al., 2014).

In addition to its mood-stabilizing properties lithium has a distinctive, independent and proven anti-suicide action (Barjasteh-Askari et al., 2020; González-Pinto et al., 2006; Smith et al., 2017; Song et al., 2017). This is a relevant quality in BD, since up to 15% of patients diagnosed with BD die by suicide (Gordovez et al., 2020). In fact, a systematic review and meta-analysis showed that treatment with lithium among people with mood disorders could reduce the risk of death and suicide up to 60% compared to placebo (Cipriani et al., 2013). Remarkable neuroprotective and antiviral properties have also been attributed to lithium (Post, 2017; Rybakowski, 2018; Murru et al., 2020; Van Gestel et al., 2019). It slows brain aging (Van Gestel et al., 2019) and reduces the risk of dementia by almost 50% in patients with BD (Velosa et al., 2020). In addition, it could attenuate cognitive and functional decline in patients (without BD) with mild cognitive impairment (Forlenza et al., 2019). Moreover, the use of lithium has recently been proposed as a potential treatment for CoViD-19 (Murru et al., 2020).

Despite the undeniable evidence in favour of its application in BD, a descendent tendency in the use of lithium has been noticed in the US (Rhee et al., 2020) and in numerous European countries (Bohlken et al., 2020; Karanti et al., 2016; Kessing et al., 2016; Lyall et al., 2019). In several of them it has changed from being the most prescribed drug to the least one, even behind the controversial antidepressants. (Kessing et al., 2016; Lyall et al., 2019). The emergence of new effective drugs for BD, such as second-generation antipsychotics and certain anti-epileptics have overturned the prescription pattern of BD (Malhi et al., 2020; Anmella et al., 2020). The absence of pharmaceutical marketing, the toxic perception of its adverse effects, the slow onset of action and the need for venipuncture monitoring are some of the possible causes of this declining trend (Gitlin, 2016a; Rybakowski, 2018). Neither the main clinical guidelines nor current scientific literature support the idea of replacing lithium by other drugs. In fact, over the last two decades, the decrease in lithium's use is not widespread and in certain countries the lithium's prescription rate has remained high. In some countries, more than 50% of bipolar patients are treated with lithium while in the US for example, only the 17% (Kessing et al., 2019; Parabiaghi et al., 2015; Renes et al., 2018, Rhee et al., 2020) (Table 1).

In this context, an anonymous survey was carried out among psychiatrists. The primary objective of this study was to evaluate the use and the current perception of lithium's treatment on the most relevant aspects of the drug: indication, dosage, monitoring and information for patients. The results that are presented below could be used for the elaboration of new consensus or national protocols, which in turn will promote and optimize the use of lithium in our country.

Table 1

Changes in the lithium prescription rate in several European countries over the last two decades.

Study	Country	Period	Data source	Results
Bohlken et al., 2020	Germany	2009–2018	Neuropsychiatric private practices' records	The percentage of patients with bipolar disorder receiving lithium declined from 31,4% (2009) to 26,2% (2018)
Rhee et al., 2020	United States	1997–2000 vs. 2013–2016	Outpatient physician reports of patient visits	The percentage of patients with bipolar disorder receiving lithium declined from 30,4% (1997–2000) to 17,6% (2013–2016)
Lyall et al., 2019	Scotland	2009–2016	Records of outpatient clinic attendance, general/acute hospital admissions and psychiatric hospital admissions	The percentage of patients with bipolar disorder receiving lithium declined from 26% (2009) to 22% (2016)
Renes et al., 2018	Netherlands	2009–2014	Outpatient psychiatrists' and patients' surveys	Lithium was used by 70% of patients with bipolar disorder or schizoaffective disorder, bipolar type
Karanti et al., 2016	Sweden	2007–2013	Records of private and public psychiatric outpatient health care units	The percentage of patients with bipolar disorder receiving lithium declined from 51% (2007) to 41% (2013)
Kessing et al., 2016	Denmark	2000–2011	Records of all Danish patients with a first-ever contact with mental healthcare	The one-year prescription rate of lithium in bipolar patients decreased from 41% (2000) to 34% (2011)
Parabiaghi et al., 2015	Italy	2000–2010	A population-based database of dispensing records	The prevalence of lithium treatment grew by 38% during the observation period
Hayes et al., 2011	England	1995–2009	Records of primary care patients	The prescription rate for lithium increased from 22.5% (1995) to 29.3% (2009)
Castells et al., 2006	Spain	1985–2003	Pharmacy sales data of medicinal products	Lithium daily dose per 1000 inhabitants per day (DID) increased from 0.21 (1985) to 0.79 (2003)

Methods

Study design and sample

Between 11 May and 11 July 2020 an online anonymous survey was conducted on the use of lithium thanks to the support of the Spanish Society of Biological Psychiatry (SEPB). All the members of the SEPB (500 psychiatrists) received an email in which they were informed about the purpose of the study. They were invited to participate in it by completing the questionnaire attached to the same message. The collaboration was voluntary and responses were recorded eliminating the identity of the participants. To maximize the response rate, two reminder emails were sent during the mentioned period. The survey was created and performed with Google Forms and Microsoft Office Excel 2019 was used for the analysis and representation of the data. The study was approved by the Research Ethics Committee of Basque Country (Spain).

Questionnaire

The survey was designed to obtain the general perspective on lithium's use from a sample of Spanish psychiatrists. In order to encourage participation, a brief self-administered questionnaire (21 items) with multiple-choice questions (Annex 1) was elaborated. The first 5 questions are related to demography: age, sex and origin of the respondents. The following 3 points address the prescription rate of lithium in BD and the main reasons not to prescribe it. The next 5 requests explore its status compared to the rest of the drugs and the stage in the course of the illness when lithium is usually introduced. Subsequently, there are 2 specific questions about two practical and relevant aspects of lithium's use: plasma concentrations and dose distribution. The next 4 refer to the use of lithium in special clinical circumstances (minors, elderly and psychiatric comorbidity). The final issues are about the availability of official documents or protocols to monitor and inform patients undergoing lithium treatment.

Analysis

Data are analyzed using descriptive statistics. The results are represented by graphs based on percentages and absolute numbers. Microsoft Office Excel 2019 is used for the analysis and the representation of the data.

Results

Demographics

A total of 212 responses are obtained from almost all regions of Spain (Fig. 1). The majority of respondents (70%) come from Catalonia (28%), the Community of Madrid (27%) and the Basque Country (15%). The distribution between sexes and age groups is practically homogeneous as it is the percentage of professionals who work at hospitals (psychiatric or general) and outpatient settings (Table 2).

Table 2
Demographic profile of the participants.

Profile of psychiatrists	n (%)
Sex	
Man	100 (47%)
Woman	112 (53%)
Age range	
25–35	54 (26%)
36–45	57 (27%)
46–55	42 (20%)
56–65	39 (18%)
> 65	20 (9%)
Work center	
General hospital	88 (41%)
Psychiatric hospital	23 (11%)
Outpatient consultation	101 (48%)
Total	212 (100%)

Lithium's prescription and reasons not to use it

Only 3% of respondents never prescribe lithium salts. 70% of participants prescribe lithium to more than 50% of patients diagnosed with BD and 20% to more than 75% (Annex 2. Figure 1).

Almost 62% of psychiatrists affirm that the main reason not to prescribe lithium are its side effects. A significantly lower percentage of specialists state that the main cause not to prescribe it is the rejection by the patient (13%) and the need for monitoring by venipuncture (10%) (Fig. 2).

Over 75% of the participants choose lithium as the first option in the maintenance treatment of BD both in women and men (Annex 2. Figure 2). As a second option, antipsychotics (34%) and valproate (31%) stand out in women. For men, valproate (64%) is clearly the second preferred option.

Finally, more than 80% of respondents usually initiate treatment with lithium salts after the first affective episode. Most of them prescribe it after the first manic episode. More than 25% of psychiatrists when there is a family history of BD tend to start lithium treatment after the first depressive episode (Table 3).

Table 3
The time when lithium is started in BD.

After the 1st manic episode	111 (52,5%)
After the 1st depressive episode with family history of BD	8 (4%)
In the two previous situations	51 (24%)
During the first 5 years of the disease	28 (13%)
Between the first 5–10 years of the disease	6 (3%)
10 years after the onset of the disease	1 (0,5%)
I do not prescribe lithium	7 (3%)
Total	212 (100%)

Serum levels and dose distribution

50% of the participants use serum lithium levels between 0.6–0.8 mmol/L for the maintenance phase of BD. 21% consider adequate any concentration within the therapeutic range established between 0.6–1.2 mmol/L. Another 20% utilizes higher lithium serum levels between 0.8-1 mmol/L to prevent relapse or recurrence in BD (Fig. 5).

Regarding the distribution of the lithium's dose, more than 75% of psychiatrists prescribe it in 2 daily doses. 13% in 3 daily doses and only 9% in a single daily dose (Fig. 3).

Specific populations

60% of respondents (128) do not deal with children and adolescents. Among the psychiatrists who care for underage BD patients, the majority (57%) do not use lithium salts in this population (Table 4). By contrast, the majority of survey respondents do use lithium in older age BD (Table 4).

Over 80% of specialists do not have any trouble prescribing lithium to patients with a comorbid Substance Use or a Personality Disorder (Table 4).

Table 4
The use of lithium in specific populations with BD.

	N	%
Children and adolescents		
YES	36	43%
NO	48	57%
Older adults		
YES	145	76%
NO	45	24%
Substance Use Disorder		
YES	148	81%
NO	35	19%
Personality disorders		
YES	172	86%
NO	29	14%

Information for patients and monitoring protocols

One third of psychiatrists who prescribe lithium do not have documentation for patients at their workplace. Furthermore, a quarter of respondents do not follow a formal protocol for monitoring lithium and its adverse effects (Annex 2. Figure 3).

Discussion

This is the first study referring to the use of lithium that analyzes the current general perspective of psychiatrists. In 2018, an interesting international survey was published focused exclusively on lithium's monitoring (Nederlof et al., 2018). In order to understand the international framework of lithium's underuse it is essential to know the point of view of the specialists (Malhi, 2020).

According to the results of the National survey on the use of lithium, the vast majority of Spanish psychiatrists in this sample, which includes professionals from all the autonomous communities comply with the recommendations of the latest clinical guidelines and the scientific literature. 70% of the survey respondents prescribed lithium to more than 50% of patients diagnosed with BD and 20% to over 75%. In this line, more than 75% of national psychiatrists who participated in this study chose lithium as their first-choice treatment in the maintenance phase of BD both in men and women.

The apparently high prescription of lithium by Spanish psychiatrists agrees with the results that have recently been observed in the Netherlands, where 70% of patients diagnosed with BD or Schizoaffective Disorder were treated with lithium (Renes et al., 2018). Nevertheless, as it is mentioned above this percentage is significantly higher than in other neighboring countries (Kessing, 2019). In Sweden, the prescription rate for lithium in BD is 55%, in Denmark 41.7%, in Germany 26.2% and in Scotland 22% (Bohlken et al., 2020; Karanti et al., 2016; Kessing et al., 2016; Lyall et al., 2019) (Table 1).

In the current study, we asked participants about the reasons not to prescribe lithium in the long-term treatment of BD. Most agree that lithium's adverse effects are the main barrier for its use. Only 6% of the participants believe that the non-prescription of lithium is due to the availability of other more effective mood stabilizers. This fact shows the conviction that participating psychiatrists have in the efficacy of lithium above other effective drugs. Practical aspects related to the use of lithium, such as the need for monitoring or the slow onset of action are not considered obstacles for the prescription of the drug. As suggested for clozapine (Bachmann et al., 2017; Verdoux et al., 2018) the high use of lithium in Spain could be the consequence of a local "culture" that favors the use of the drug. This could be because of the transmission of personal experience from expert therapists to beginners, institutional support that facilitates the adequate infrastructure for the follow-up of patients on lithium treatment (lithium clinics and national registries, for example) and the promotion of its use by scientific societies. Knowing exactly why lithium is not prescribed in other countries would help to understand better its international underuse.

Despite the fact that most of the professionals believe that the side effects of lithium are the main limiting factor for its prescription, more than 75% consider it the first-choice treatment for the maintenance therapy of BD for both women and men. In recent years, it has been confirmed that the most serious adverse effects of lithium, that is, kidney dysfunction and teratogenic risk were overestimated in the former reports (Fornaro et al., 2020; Nielsen et al., 2017). Additionally, the risk of suffering from both complications can be minimized by using a minimum effective dose and a close monitoring of plasma levels (Tondo et al., 2019).

Therapeutic alternatives to lithium are not exempted from significant risks. Valproate has a high teratogenic risk which discourages its use in fertile women (EMA, 2018; Anmella et al, 2019). That is why it is striking the relatively high percentage of psychiatrists (31%) who choose valproate as a second option for women suffering from BD. On the other hand, antipsychotics are associated with a greater weight gain and a worse metabolic profile than lithium (Hayes et al., 2016; Jauhar and Young, 2019). Besides, they can cause extrapyramidal and sexual symptoms too (Huhn et al., 2019). Although it is clear that there is a reasonable concern about its negative effects, these data would explain the high percentage of psychiatrists who choose lithium as the first option for the long-term treatment of BD in both sexes. Moreover, lithium has potential long-term benefits related to neurogenesis that are being studied (Berk et al., 2017b; Forlenza et al, 2019; Sun et al., 2019; Zanni et al., 2019; Ciftci et al., 2020). Emphasizing the benefits of lithium without forgetting its adverse effects (Gitlin, 2016b; Tondo et al., 2017) could help improve the outcome of patients with BD.

The most used serum lithium levels for the maintenance treatment of BD (0.6–0.8 mmol/L) are also in line with current scientific advice (Nolen et al., 2019). This is a crucial issue because the use of conservative plasma levels could prevent lithium intoxication, renal and central nervous system adverse effects (Nielsen et al., 2018; Schoot et al., 2020). Another practice that could minimize the risk of renal negative effects is the schedule of a single lithium daily dose (Schoot et al., 2020). However, this regimen is the least used among the respondents who prefer to distribute lithium dosage in 2 or 3 daily doses.

Another point that differs from the latest scientific publications is the little use of lithium among children and adolescents with BD. Most psychiatrists who take care of minors (57%) do not use lithium when the literature suggests that it is an effective and safe treatment in this population (Amerio et al., 2018; Hafeman et al., 2019). Taking into account that the typical onset of the disease is in adolescence and due to the dividing line between child and adult care in Spain, it can be difficult to supply lithium since the first episode.

Finally, it must be stated that the availability of official documentation on lithium for patients (67%) and protocols for its monitoring (72%) is similar to the mentioned international study (Nederlof et al., 2018). The publication of expert consensus, such as the one which has recently been prepared by the SEPB (González-Pinto et al., 2020) are initiatives that help to improve these figures.

This study has several strengths and limitations. As underlined before, this is the first research that evaluates the general perspective on the use of lithium among a large group of psychiatrists. The fact that 70% of the responses come from 3 autonomous communities limits the generalization of the results to the whole country. Nonetheless, they are three of the most populated autonomous communities, especially Catalonia and the Community of Madrid. Furthermore, these 3 regions attract specialists trained in other territories because of their greater job offer. The number (212) and the rate (42,5%) of responses are higher or similar to other surveys addressed to professionals (Campos et al., 2020; Daod et al., 2019; Nederlof et al., 2018). The social desirability and selection bias could have overestimated the use of lithium in our country. The survey was distributed only among members of a single national society of Psychiatry not considering the perspective of psychiatrists who are not members of the SEPB. As part of SEPB, members might be exposed to a more continuous update and training on guidelines due to the continuous education and training opportunities offered within the society. Finally, the present study does not analyze national prescription registers. Thus, it would be interesting to complement the current essay with a pharmaco-epidemiological analysis, such as those carried out in other countries that have already been pointed out (Table 1). It should be noted, though, that the results obtained in this study are congruent with the pharmaco-epidemiological research performed in other countries (Parabiaghi et al., 2015; Renes et al., 2018) and with the only one published in Spain (Castells et al., 2006).

Conclusions

The results of this survey suggest that, at least in Spain, the use of lithium is consistent with the latest clinical guidelines. Based on these results, and except for children and adolescents, which requires further

study, one cannot speak of an underuse of lithium in Spain. The use of valproate as one of the main alternatives to lithium in women is one of the few matters that differ from the recommendations of the main scientific societies. The main barrier to prescribe lithium is its side effect profile. Behind this apparent high use of lithium could be a local culture that favors the dissemination of scientific and practical information about the drug.

Abbreviations

BD

Bipolar disorder.

Declarations

- **Ethics approval and consent to participate**
- The study was approved by the Research Ethics Committee of Basque Country (Spain).
- **Consent for publication**
 - Respondents authorized the use of their data based on current legislation on the protection of personal data.
- **Availability of data and material**
 - The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- **Competing interests**
 - EV has received grants and served as consultant, advisor or CME speaker *unrelated to the present work* for the following entities: AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, Sunovion, and Takeda.
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- **Authors' contributions**
 - XPM and AG-P performed the survey, analyzing, writing, and editing the data.
 - DH-M and EV provided critical appraisal of the manuscript.

- All authors read and approved the final manuscript.
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Figures

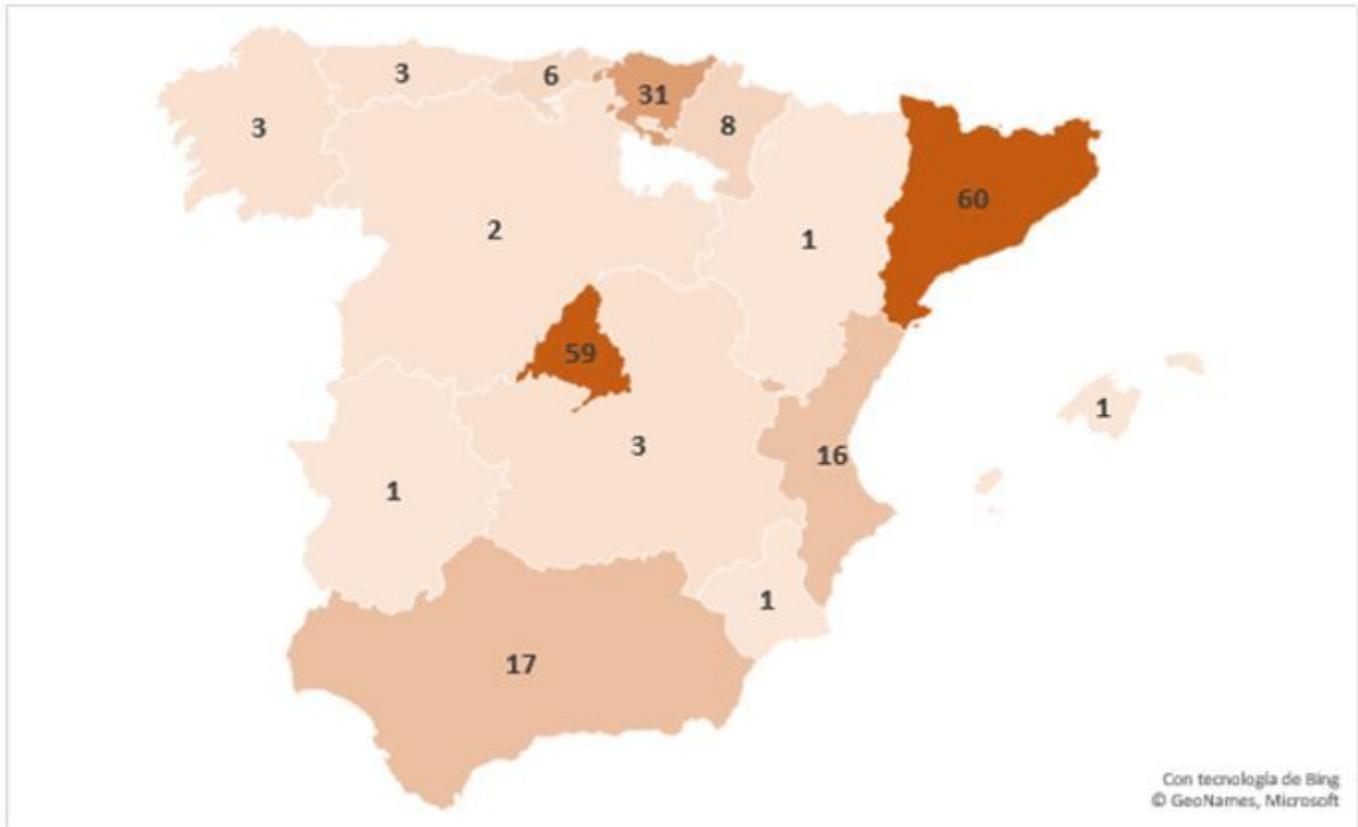


Figure 1

Number of responses in each Autonomous Community. Only regions with data are displayed. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

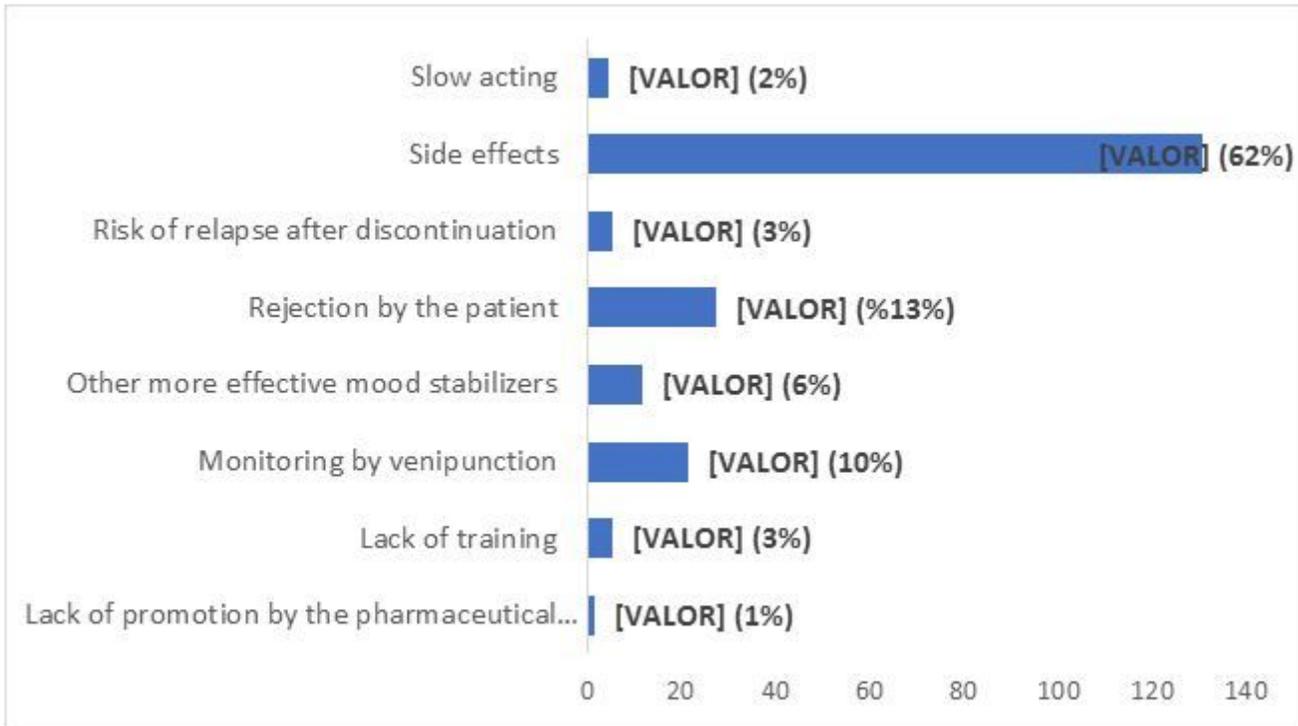


Figure 2

Main reasons not to prescribe lithium.

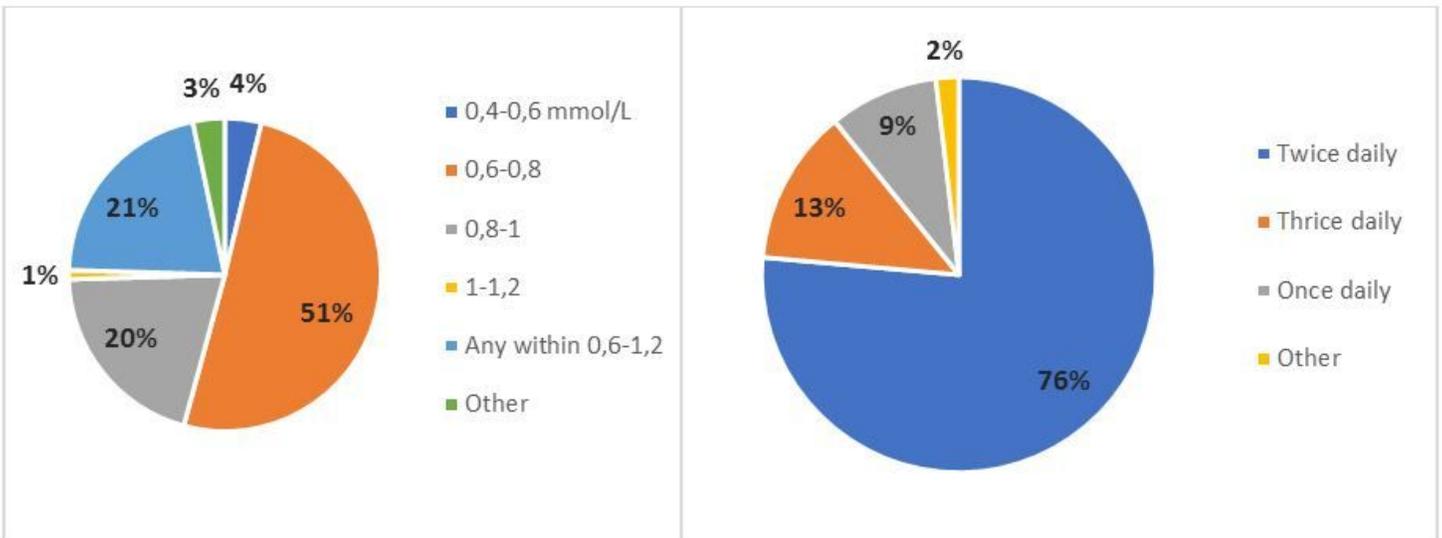


Figure 3

The preferred serum level and dose distribution of lithium.

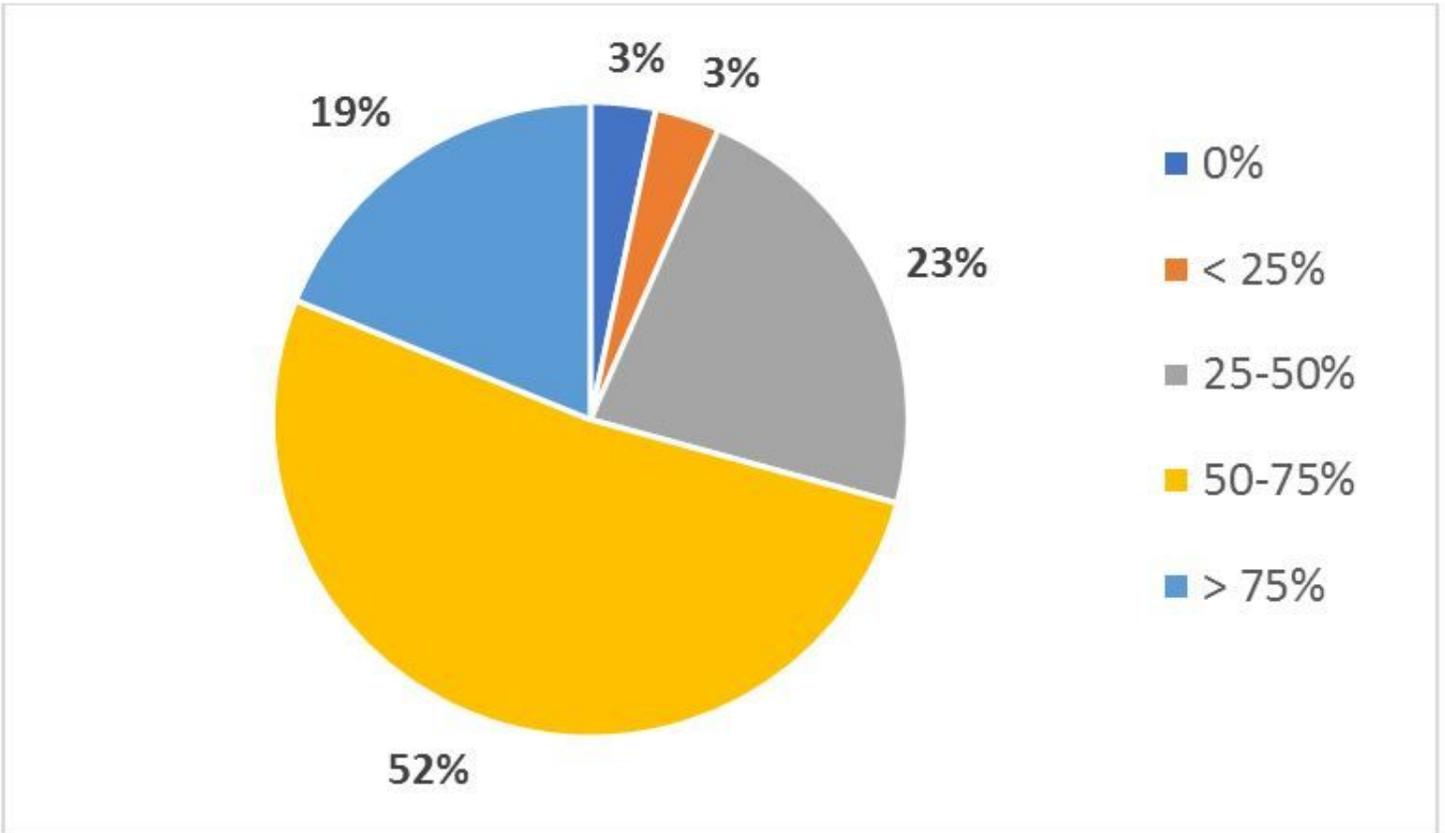


Figure 4

Percentage of patients with BD who are treated with lithium.

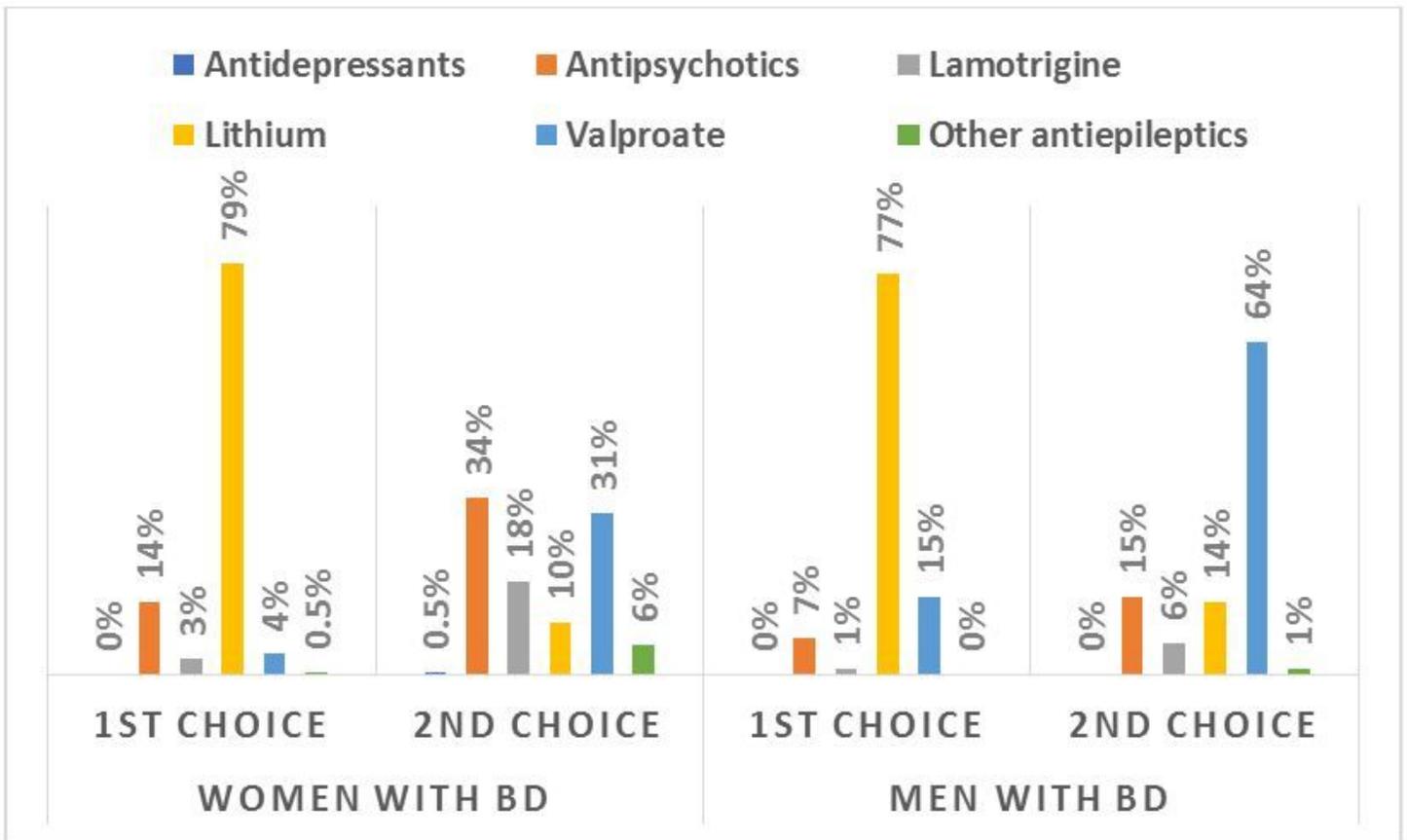


Figure 5

The preferred treatments for maintenance therapy in BD.

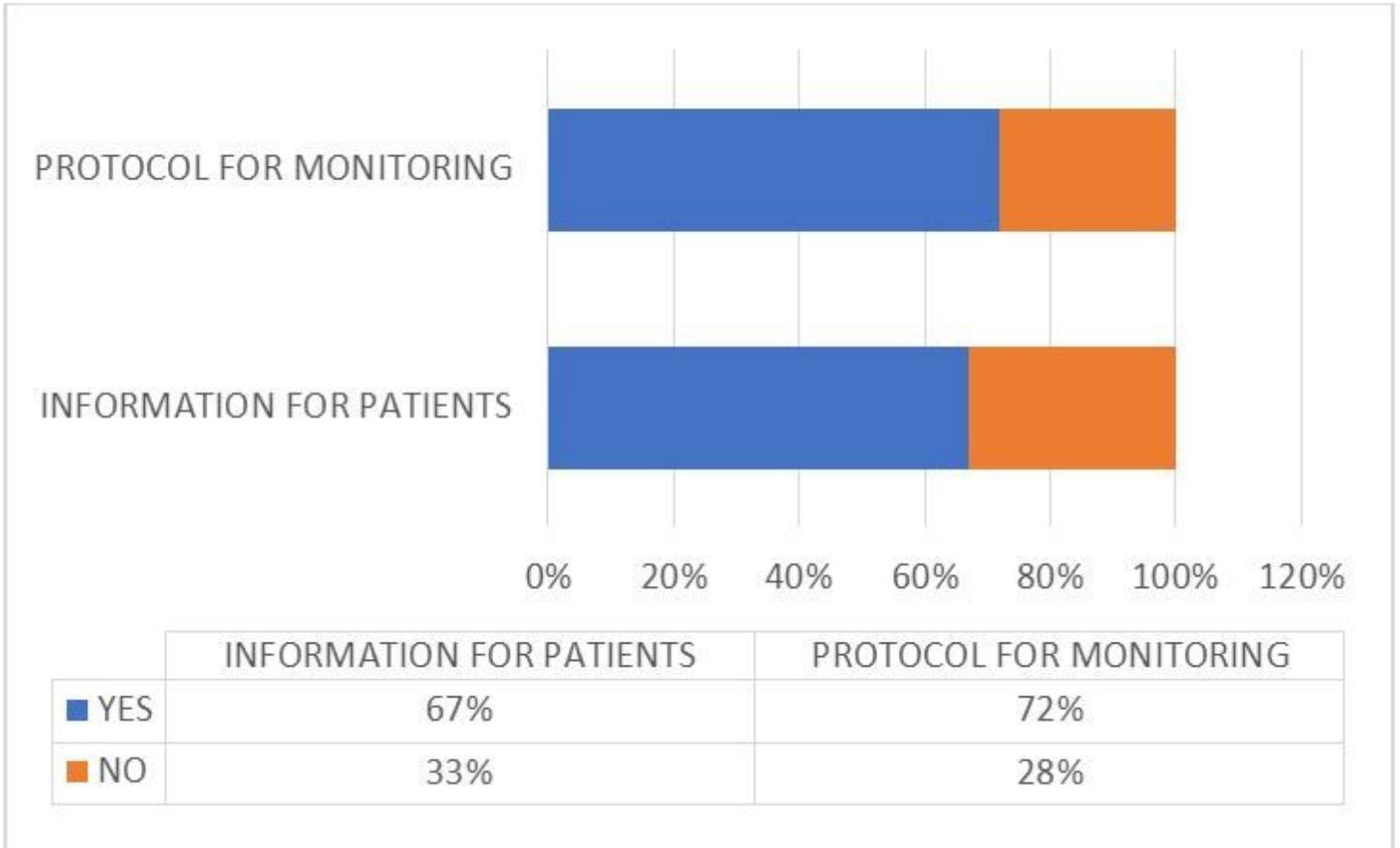


Figure 6

Availability of official documentation.